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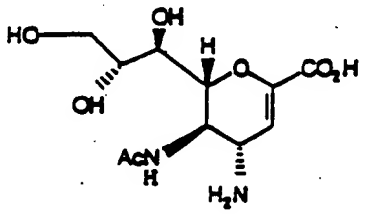
(54) Title: PREPARATION OF N-ACETYL NEURAMINIC DERIVATIVES



(III)

(57) Abstract

Processes for the preparation of 4-substituted analogues of 5-acetylamino-2,3,5-trideoxy-D-glycero-D-galacto-non-2-eno-pyranosinic acid are described.

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PREPARATION OF N-ACETYL NEURAMINIC DERIVATIVES

The present invention relates to a process for the preparation of derivatives of N-acetyl neuraminic acid. More particularly the invention relates to a process for the preparation of 5-acetamido-4-amino-2,3,4,5-tetradeoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (the 4-amino analogue of DANA; also known as 5-(acetylamino)-4-amino-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid) and derivatives thereof and the preparation of intermediates for use in the process.

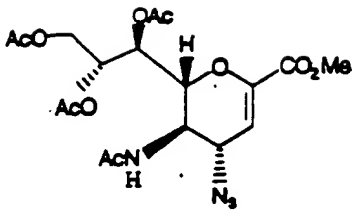
Schreiner et. al. Ann. Chem 1991, 129-134 describe the preparation of the 4-amino analogue of DANA from the peracetylated methyl ester of sialic acid (peracetyl NANA methyl ester) by the route shown in Scheme 1.

PCT/AU91/00161 (publication no. WO91/16320) describes a number of derivatives of 5-acetamido 2,3,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (2,3-dideoxy-2,3-didehydro-N- acetyl-neuraminic acid; DANA) including the 4-amino analogue of DANA from the peracetylated methyl ester of DANA by a method similar to that of Schreiner et. al. with the exception that the peracetylated compound (3a) was reduced prior to deacetylation. The method is shown in Scheme 2.

A major problem with the known processes for preparing the 4-amino analogue of DANA lies in the fact that the conversion directly or indirectly of the compound (2) and any other compound with a leaving group in the 4-position with azide is not stereospecific and leads to significant amounts of the undesired ß-isomer (3b) in addition to the desired α-isomer (3a). This leads to both reduced yields of the desired compound and to the need for chromatographic purification at this or a subsequent step in the synthesis.

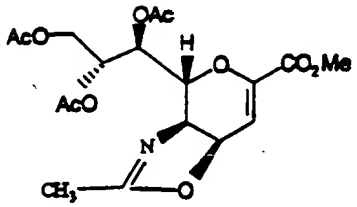
We have now found that by careful selection of the azide source the conversion of (2) to (3a) can be effected with high stereospecificity.

The invention thus provides in a first aspect a method for the preparation of the compound of formula (I)



(I)

by reaction of the compound of formula (II)



(II)

with trimethylsilylazide ($TMSN_3$).

It is currently believed that the reason for the stereospecificity is that the reaction generates HN_3 in situ: other reagents which generate HN_3 in situ are well known to those skilled in the art.

The reaction is effected in a protic solvent. Preferably the solvent is a C_{1-4} alcohol in particular a hindered alcohol. Hindered alcohols include for example isopropyl alcohol and, particularly, tert-butyl alcohol.

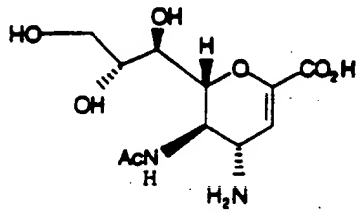
The reaction is conveniently carried out at a temperature of for example 0-150°C, preferably at 15-90°C such as about 80°C. Conveniently the reaction will be effected at below the reflux temperature of the selected solvent.

The amount of $TMSN_3$ employed will generally be in the range of from about 1 to about 6 molar equivalents of the compound of formula (II), preferably 1.5 to 2 molar equivalents.

A significant problem also arises with the reduction of compounds such as (3a) and (4), there being a risk of undesired reduction of the 2,3-double bond in addition to reduction of the azido group. Such potential for over-reduction leads both to reduced

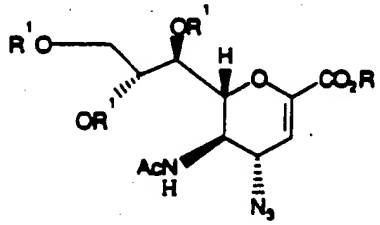
yield and to the presence of by-products which necessitates more extensive purification procedures. We have now found that yield and purity of the 4-amino analogue of DANA can be improved by reducing the compound (4) or a protected derivative thereof in the presence of certain catalysts.

The invention thus provides in a second aspect a method for the preparation of the compound of formula (III)



(III)

which comprises catalytic hydrogenation of a compound of formula (IV)



(IV)

(wherein R is H or a C_{1-4}alkyl group and R^1 is H or a hydroxyl protecting group for example an acyl group such as acetyl) followed where required by hydrolysis.

The compound of formula (IV) may optionally be protected by any suitable hydroxyl protecting groups for example as described in 'Protective Groups in Organic Synthesis' by Theodora W. Green (John Wiley & Sons, 1981) which also describes methods for the removal of such groups.

It will be appreciated by those skilled in the art that where R and/or R^1 in compound (IV) are other than hydrogen partial removal of the protecting groups and/or hydrolysis of the C_1- ester may occur during the reduction phase. However, upon hydrolysis all such partially hydrolysed compounds will be converted to the compound of formula (III).

The solvent for use in the reduction step may be either an aqueous solvent comprising water or a mixture water and any compatible organic solvent miscible with water or an organic solvent such as an ether, lower alcohol or the like. Preferably the solvent is water.

Preferably the catalyst is a poisoned catalyst but in particular a poisoned palladium catalyst. A particularly preferred catalyst is a Pd catalyst poisoned with lead, for example a Lindlar catalyst.

The reduction is conveniently carried out 0-50°C, preferably at ambient temperature.

The hydrolysis may be effected by any suitable base and is preferably effected in an aqueous medium. Suitable bases include aqueous triethylamine, NaOH, Na_2CO_3 and the like. Where protecting groups are present appropriate deprotection agents known in the art may be employed.

In a preferred embodiment the invention comprises the preparation of the compound of formula (III) as defined herein from the compound of formula (II) by the steps of :-

(a) reacting the compound of formula (II) with HN_3 to give a compound of formula (I)

(b) hydrolysing the compound of formula (I) to give a compound of formula (IV); and

(c) hydrogenating the compound of formula (IV) in the presence of a poisoned catalyst followed by hydrolysis.

The 4-amino analogue of DANA is a potent inhibitor of the influenza virus both in vitro and in vivo and is thus useful in the treatment of viral infections such as influenza. (see for example WO91/16320).

The 4-amino analogue of DANA is also of use as an intermediate in the synthesis of other DANA derivatives which are inhibitors of the influenza virus (see for example WO91/16320).

The invention is illustrated by the following non-limiting examples. All temperatures are in °C.

Intermediate 1

A 3 litre 3-necked round bottomed flask equipped with a water condenser and presure equalised dropping funnel was charged with a solution of methyl 5-acetamido-2,4,7,8,9-penta-O-acetyl-D-glycero-D-galacto-2-nonulopyranosonate (peracetyl NANA methyl ester) (70g) in dichloromethane (1050ml). Trimethylsilyl trifluoromethanesulfonate (76ml) was then added dropwise over 10 min. with stirring (magnetic stirrer) under an inert atmosphere of nitrogen. After the addition was complete the oil-bath temperature was raised over 25 min to ca. 50°C. After 4.5 h at reflux the reaction mixture was allowed to cool and poured into a vigorously stirred mixture of aqueous sodium hydrogen carbonate (1700ml), ice (500ml) and solid sodium hydrogen carbonate (80g). After ca. 10min. the solution was checked to confirm that it was still basic (pH=8) and the organic phase separated off. The aqueous phase was further extracted with dichloromethane (3 times 500ml) and the combined extracts were treated with Norit ultra SX + charcoal, dried ($MgSO_4$) and evaporated in vacuo at 48 - 50°C (rotary evaporator) to give methyl 7,8,9-tri-O-acetyl-2,3-didehydro-2,3,5-trideoxy-4',5'-dihydro-2'-methyloxazolo[4,5-d]-D-glycero-D-talo-2- nonulopyranosidonate (52.5g).
TLC : (Silica gel - Ethyl acetate : single spot Rf = 0.55 (visualised with UV and ceric sulphate spray)

NMR : δ($CDCl_3$) 2.15-2.0 4xs each 3H, 3.44 dd 1H, 3.81 s 3H, 3.96 dd 1H, 4.22 dd 1H, 4.60 dd 1H, 4.82 dd 1H, 5.44 m 1H, 5.64 m 1H, 6.38d 1H.

Example 1

(i) A 3-necked round bottomed flask equipped with a water condenser and pressure equalised dropping funnel was charged with a solution of Intermediate 1 (7.8g) in t-butanol (65ml). Heating of the stirred solution (magnetic stirrer) to 80°C was then commenced while azidotrimethylsilane (10.5ml) was added dropwise over 3.5 h.

After a total of 4h the reaction mixture was allowed to cool and poured into a vigorously stirred mixture of aqueous sodium hydrogen carbonate (350ml), (chilled in an

ice bath) and solid sodium hydrogen carbonate (10g). After ca. 5min. the soluti n was extracted with ethyl acetate (3 times 150ml). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo at 48 - 50°C (rotary evaporator) to give crude compound 3a, methyl 5-acetamido-7,8,9-tri- O-acetyl-4-azido-2,3-didehydro-2,3,4,5-tetradeoxy-D-glycero-D- galacto-2-nonulopyranosidonate (8.027g).

TLC : (Silica gel - Methanol (1) / $CHCl_3$ (19)): Rf 0.1 (visualised with UV and Ceric sulphate spray)

NMR : δ($CDCl_3$) 2.14 - 2.00 4xs each 3H, 3.82 s 3H, 3.88 m 1H, 4.21 m 1H, 4.51 m 2H, 4.64 dd 1H, 5.34 m 1H, 5.47 m 1H, 5.82 d 1H, 6.00 d 1H.

(ii) To a stirred solution of the product of step (i) (7.51g) in dry methanol (17ml) under an inert atmosphere of nitrogen was added 1% sodium methoxide (10ml). The mixture was stirred at 21°C for ca. 30 min. Dowex 50Wx8 (H+) resin (ca 7g) was added to adjust the pH to 7. The solvent was then filtered and the resin further washed with methanol (4x20ml). The combined filtrates were evaporated under reduced pressure (rotary evaporator) at 48 - 50°C to give compound 4b, methyl 5-acetamido-4-azido-2,3-didehydro-2,3,4,5-tetradeoxy-D- glycero-D-galacto-2-nonulopyranosidonate (5.03g) as a buff foam.

TLC : (Silica gel - Methanol (1) / CHCl3 (3)): Rf 0.025 (visualised with UV and Ceric sulphate)

NMR : δ(D_2O) 2.06 s 3H, 3.60-3.99 m 4H, 3.84 s 3H, 4.20-4.46 m 3H, 6.10 d 1H.

Example 2

A 20L 4 necked round-bottomed flask was equipped with a thermometer, an overhead air driven teflon stirrer and a condenser. The flask was immersed in a steam heated water bath. Hot water (50°) was circulated through the condenser. Nitrogen was passed through a combined inlet/outlet fitting at the top of the condenser to blanket the reaction and to flush any low boiling vapours through to a train of scrubbers containing

sodium hydroxide solution (~2M) in two, and ceric ammonium nitrate solution (1% w/v) in the third final scrubber.

The reaction flask was charged with Intermediate 1 (1.5kg) and tert.butanol (11L). Trimethylsilyl azide (724 ml) was added and the stirred mixture was heated to reflux under the nitrogen blanket for 10h. and left to cool overnight in the water bath.

A solution of sodium nitrite (300g) in water (1.5l) was added. The reaction mixture was cooled to <20°, the nitrogen blanketing was stopped and the top of the condenser was connected directly to the scrubber system.

Hydrochloric acid solution (~6M; 625ml) was added dropwise over 1h with continued cooling to maintain the temperature below 20°, and to control the gas evolution. The mixture was stirred for 2 h after gas evolution had ceased.

The mixture was transferred to a 50L separator with ethyl acetate (8L) and distilled water (8L). The two layers were separated and the organic layer washed with water (2x8L). The combined aqueous layer was back extracted with ethyl acetate (5L) and separated.

The combined organic layer was washed with sodium hydrogen carbonate solution (6% w/v, 2x8L) and then with sodium chloride solution.

The separated organic layer was concentrated to a crystalline slurry (~ 1 vol) then the solid was collected by filtration, washed with water (2 x 2L) and dried in vacuo to give compound 3a, methyl-5-acetamido-7,8,9-tri-O-acetyl-4-azido-2,3-didehydro-2,3,4,5-tetradeoxy-D-glycero-D-galacto-2-nonulopyranosidonate, monohydrate (1.32kg).

m.p. 89°

N.M.R. δ ($CDCl_3$) 6.18(1H,d,9); 5.99(1H,d,3); 5.47(1H, m); 5.32(1H, m); 4.67(1H, m); 4.46(1H, m); 4.19(1H, m); 3.93(1H, m); 3.82(3H, s); 2.15(3H, s); 2.18(3H, s); 2.09(3H, s); 1.98(3H, s).

I.R. (Nujol) 3592(NH); 2120, 2087 (azide); 1752 (CO, acetate); 1732(CO, conj.ester); 1662cm^{-1} (CO, CH_3CONH-).

Water content 4% (Karl Fischer method).

Example 3

(i) A 3-necked round bottomed flask equipped with a gas inlet tube extending below the level of liquid and a gas outlet adaptor was charged with a solution of compound 4, prepared as described in Example 1, step (ii) (2.0g) in water (50ml). Lindlar catalyst (0.2g) was then added and the flask flushed with nitrogen. Hydrogen was then bubbled through the vigorously stirred solution for 4h. Additional catalyst (0.2g) was then added at this stage and hydrogen bubbled through for a further 16h. The catalyst was then removed by filtration through celite. The filter was washed with water (2 times 50ml) and the combined filtrates evaporated under reduced pressure at 48 - 50°C (rotary evaporator) and the residue co-evaporated with methanol (3 times 50ml) to give a solid found to be a mixture resulting from partial ester hydrolysis. This material was therefore fully de-esterified without further characterisation.

(ii) A solution of the product of step (i) (1.87g) in water (20ml) was stirred at 21°C with triethylamine (5ml) for 4h. The resulting mixture was evaporated under reduced pressure at 48 - 50°C (rotary evaporator) followed by co-evaporation with methanol (2 times 100ml) to give crude product (1.81g).

(iii) A column of Dowex 2 x 8 (Cl^-) resin (100g) was converted into it's hydroxide form with 2N sodium hydroxide solution (1.5L). The resin was then washed free of hydroxide with water. Crude product from step (ii) (5.0g) dissolved in water (250ml) was then placed on the top of the column and eluted with water (400ml). Following this the resin was eluted with 1N Acetic acid solution (2L). Like fractions were combined and freeze dried to give the 4-amino analogue of DANA (2.45g). A second slightly more coloured fraction was also obtained giving after treatment as above a further quantity of the title compound (0.53g) the 4-amino analogue of DANA.

TLC : (Silica gel - nButanol (3) / Water (1) / Acetic Acid (1)): Rf = 0.22 (visualised with UV, ninhydrin and ceric sulphate)

NMR : δ (D_2O) 2.05 s 3H, 3.6-4.0 m 4H, 4.2 m 1H, 4.36 m 2H, 5.69 d 1H.

UV : (H_2O) λ_{max} 233130.7

Example 4

A suspension of compound 3a (1g), prepared as in Example 2, in water (10ml) was treated with triethylamine (1.53ml, added in 3 portions during 4½h) and the solution was left at 20° for 24h.

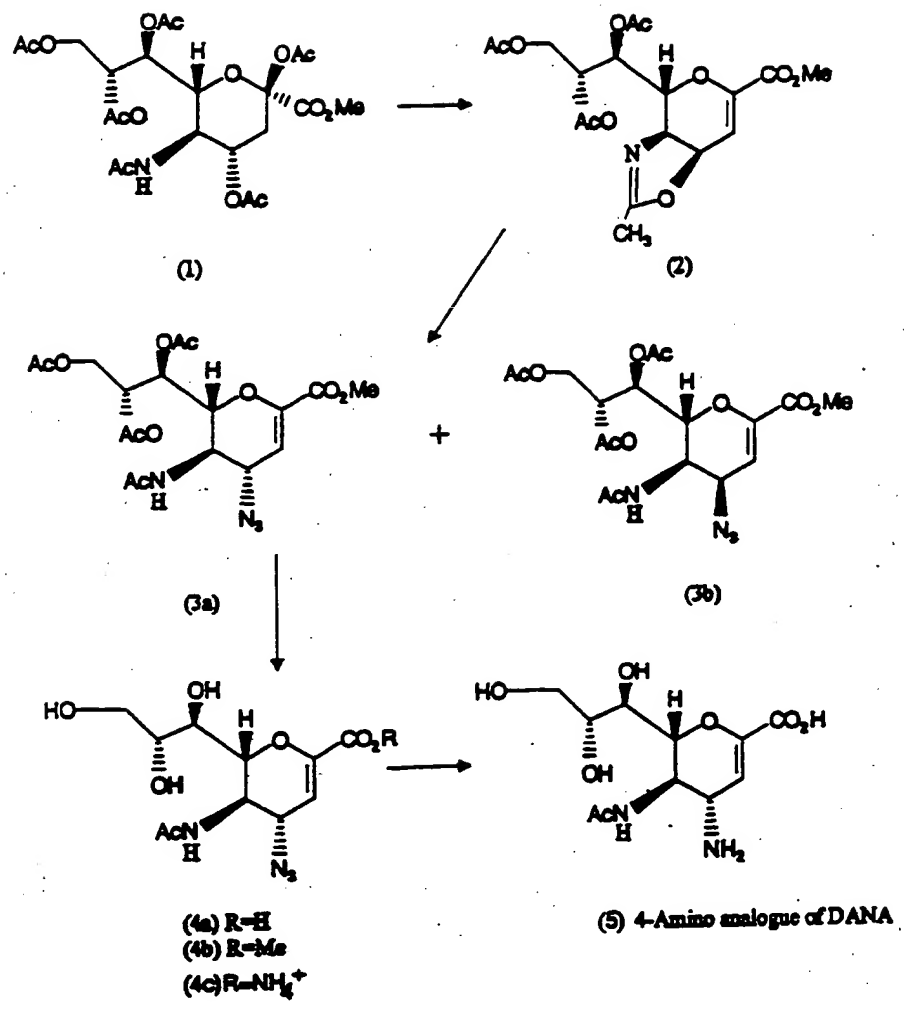
Lindlar catalyst (100mg) was added and the mixture was stirred for 6h in an atmosphere of hydrogen gas.

The catalyst was removed by filtration and the filter bed was washed with water (5 x 2ml). The combined filtrate and washings were concentrated to 3ml then isopropanol (5ml) was added portionwise. The cloudy solution was warmed and then allowed to cool, to deposit a crystalline solid. The solid was collected by filtration, washed with isopropanol (2 x 1ml) and dried in vacuo to give the 4-amino analogue of DANA (0.44g).

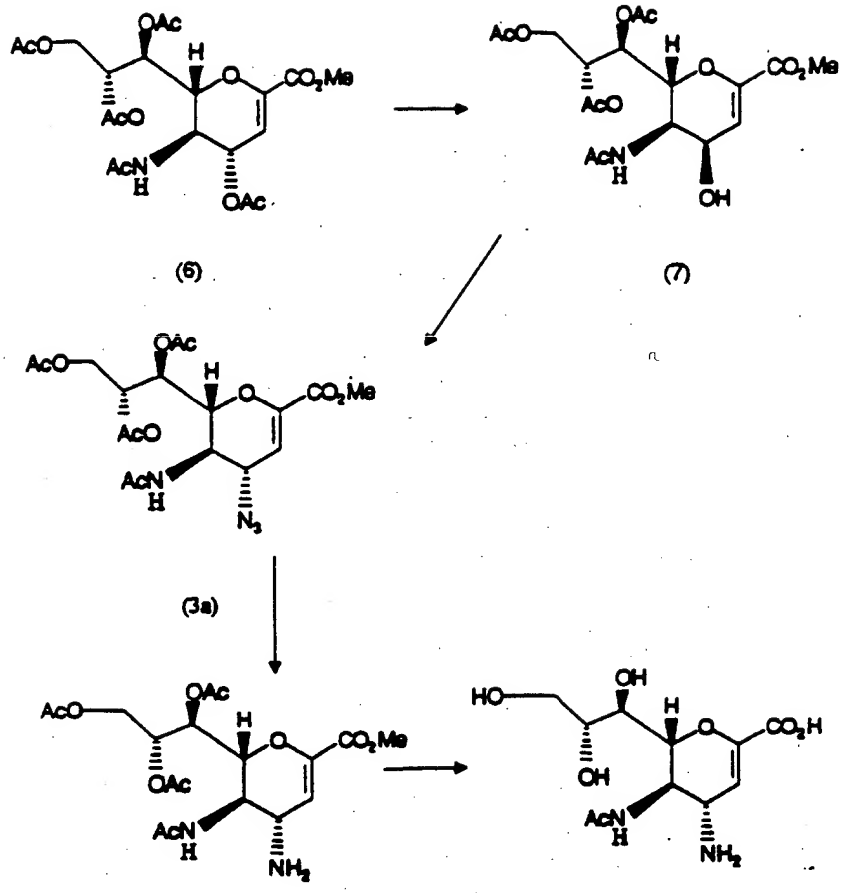
N.M.R. δ (D_2O) 5.62(1H,d,2); 4.40 - 4.25(2H, m); 4.18(1H, m); 4.05 - 3.50(4H, m).

I.R. (Nujol) 3526, 3477, 3368, 3179(OH, NH); 1675(CO, amide); 1601cm^{-1}(CO, CO_2H).

Scheme 1

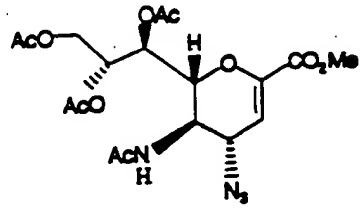


Scheme 2


AcO
OAc
H
O
CO2Me
AcO
AcN
H
OAc
OH
N3
NH2
(6)
(7)
(3a)
(8)
HO
CO2H
(5) 4-Amino analogue of DANA

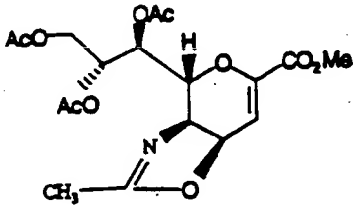
Claims

1. A process for the preparation of a compound of formula (I)



(I)

which comprises reaction of a compound of formula (II)



(II)

with HN_3.

2. A process as claimed in Claim 1 wherein the HN_3 is generated in situ.

3. A process as claimed in Claim 1 or Claim 2 wherein the compound of formula (II) is reacted with trimethylsilylazide.

4. A process as claimed in any one of Claims 1 to 3 wherein the reaction is carried out in a protic solvent.

5. A process as claimed in Claim 4 wherein the protic solvent is a C_{1-4} alcohol.

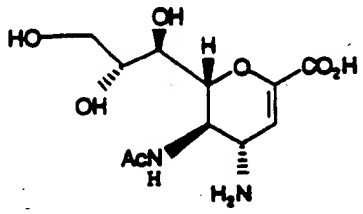
6. A process as claimed in Claim 4 wherein the reaction is carried out in tert-butyl alcohol.

7. A process as claimed in any one of Claims 3 to 6 wherein the trimethylsilylazide is present in an amount of 1 to 6 molar equivalents of the compound of formula (II).

8. A process as claimed in any one of Claims 3 to 6 wherein the molar ratio of trimethylsilylazide to the compound of formula (II) is from 1:1 to 2:1.

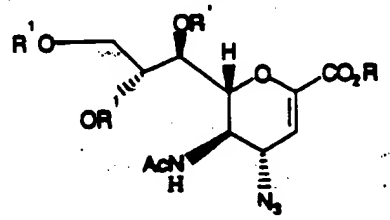
9. A process as claimed in any one of Claims 1 to 8 wherein the reaction is carried out at a temperature of from 0 to 150°C.

10. A process for the preparation of a compound of formula (III)



(III)

which comprises catalytic hydrogenation of a compound of formula (IV)



(IV)

wherein R is H or C_{1-4} alkyl and R' is H or a hydroxyl protecting group.

11. A process as claimed in Claim 10 wherein the catalyst is a poisoned catalyst.

12. A process as claimed in Claim 10 or Claim 11 wherein the catalyst is a poisoned palladium catalyst.

13. A process as claimed in any one of Claims 10 to 12 wherein the catalyst is a palladium catalyst poisoned with lead.

14. A process as claimed in any one of Claims 10 to 13 wherein the catalyst is a Lindlar catalyst.

15. A process as claimed in any one of Claims 10 to 14 which is carried out at a temperature of 0 to 50°C.

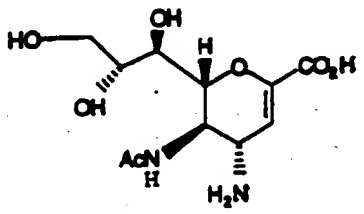
16. A process as claimed in any one of Claims 10 to 15 wherein in the compound of formula (IV) at least one of R and R' is not hydrogen and wherein the product of reduction is subsequently hydrolysed.

17. A process as claimed in Claim 16 wherein the hydrolysis is effected in aqueous medium.

18. A process as claimed in Claim 16 or Claim 17 wherein the hydrolysis is effected with a base selected from triethylamine, an alkali metal hydroxide or an alkali metal carbonate.

19. A process as claimed in any one of Claims 10 to 18 wherein the compound of formula (IV) is obtained by a method as claimed in any one of Claims 1 to 9.

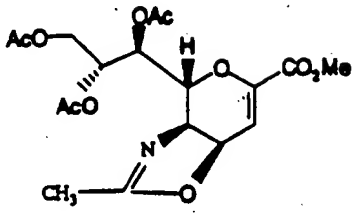
20. A process for the preparation of a compound of formula (III)



(III)

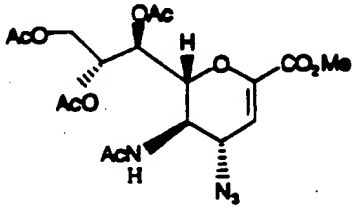
which comprises the steps of

(a) reacting a compound of formula (II)



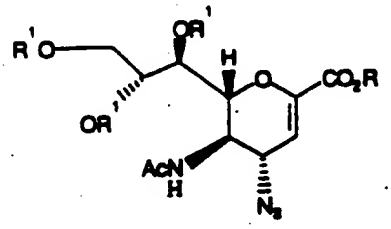
(II)

with HN_3 to give a compound of formula (I);



(I)

(b) hydrolysing the compound of formula (I) to give a compound of formula (IV)



(IV)

and

(c) hydrogenating the compound of formula (IV) in the presence of a poisoned catalyst followed by hydrolysis.

INTERNATIONAL SEARCH REPORT

PCT/EP 92/02904

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D309/28

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with Indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	LIEBIGS ANNALEN DER CHEMIE, no. 2, February 1991, Weinheim, DE, pages 129 - 134 E. FISCHER, ER AL.: 'Synthesis of some 2,3-didehydro-2-deoxysialic acids structurally varied at C-4 and their behaviour towards sialidase from Vibrio cholerae' cited in the application see schemes 1, 2; page 132, right column	1,10,20
A	WO,A,9 116 320 (BIOTA SCIENTIFIC MANAGEMENT) 31 October 1991 cited in the application see examples 1,2	1

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 FEBRUARY 1993	25.02.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	RUSSELL F. ENGLISH

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9202904
SA 67777

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 12/02/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9116320	31-10-91	AU-A-	7533891	12-12-91
		AU-A-	7759091	11-11-91
		CN-A-	1057260	25-12-91
		EP-A-	0526543	10-02-93

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82